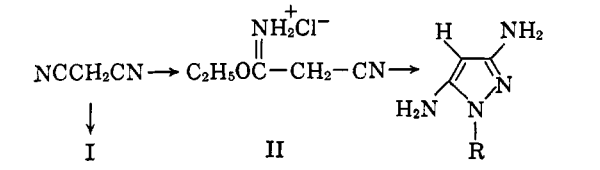
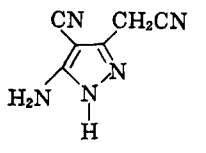
Subsequent reinvestigation by Taylor and Hartke[2] demonstrated that the actual product was 5-amino-4-cyano-3-cyanomethylpyrazole (IV), which was formed by the addition of hydrazine to the dimer of malononitrile, 1,1,3-tricyano-2-aminopropene-1. No authentic simple 3,5-diaminopyrazoles appear to have been described in the literature. An interest in new heterocyclic systems led us to investigate a synthetic route to this class of compounds.

When ethyl cyanoacetimidate hydrochloride (II)[3,4] was allowed to react with phenylhydrazine in ethanol, 3,5-diamino-1-phenylpyrazole hydrochloride (IIIb) was obtained. Similarly, the action of phenethylhydrazine on II gave 3,5-diamino-1-phenethylpyrazole hydrochloride (IIIc). Regrettably, the action of hydrazine itself on II failed; only intractable tars were formed.

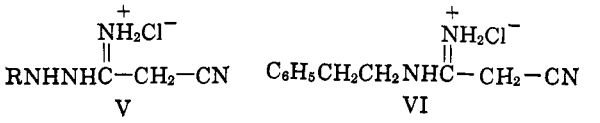


I II

IIIa, R = H
b, R = C_6H_5,·HCl
c, R = $C_6H_5CH_2CH_2$,·HCl

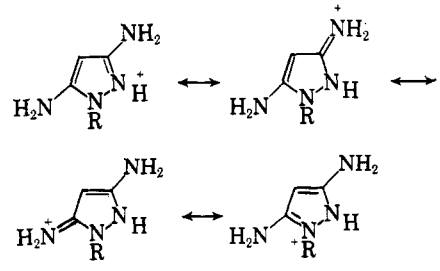


IV



V VI

Alternative structures for the products, the isomeric amidrazones V, were excluded on the basis of the n.m.r. spectra. In D_6-dimethyl sulfoxide solution, IIIb exhibits sharp singlets at 4.73 (1 proton) and 2.38 τ (5); IIIc exhibits singlets at 4.97 (1) and 2.55 τ (5), and triplets at 5.83 (2) and 7.05 τ (2). These chemical shifts differ markedly from those displayed by a reasonable model for V, cyano-N-phenethylacetamidine hydrochloride (VI).[4] The n.m.r. spectrum of VI exhibits resonance at 2.55 (5), 5.70 (2, singlet), 6.30 (2, triplet), and 7.05 τ (2, triplet). The absence of a two-proton singlet at 5.7 τ and the appearance of a one-proton singlet at 4.73 or 4.97 τ clearly excludes structure V and supports the cyclic structures IIIa and IIIb. The absence of nitrile bands in the infrared spectra of IIIa and IIIb is consistent with this interpretation.



VII

(2) E. C. Taylor and K. S. Hartke, *J. Am. Chem. Soc.*, **81**, 2452 (1959).
(3) A. H. Cook, G. Harris, and A. L. Levy, *J. Chem. Soc.*, 3227 (1949).
(4) W. J. Fanshawe, V. J. Bauer, E. F. Ullman, and S. R. Safir, *J. Org. Chem.*, **29**, 308 (1964).

Although the structures of the bases corresponding to III have been represented as 3,5-diaminopyrazoles, alternative tautomeric forms cannot be excluded. However, protonation of any tautomer can lead to VII, the most probable structure for the pyrazole salts III, in which a high degree of charge distribution is possible.

Experimental[5]

3,5-Diamino-1-phenylpyrazole Hydrochloride (IIIb).—To a solution of 7.4 g. (0.05 mole) of ethyl cyanoacetimidate hydrochloride[3,4] and 100 ml. of ethanol was added with stirring under nitrogen 5.4 g. (0.05 mole) of phenylhydrazine. After 30 min. the mixture was filtered, and the filtrate was evaporated under reduced pressure to a brown tar which crystallized from ethanol–ether. One recrystallization gave 2.3 g. (22%) of colorless needles, m.p. 230–231.5° dec. Two additional recrystallizations from ethanol–ether followed by a third recrystallization from ethanol afforded the analytical sample, m.p. 231–233° dec., λ_{max}^{MeOH} 249 mμ (ϵ 18,300).

Anal. Calcd. for $C_9H_{11}ClN_4$: C, 51.31; H, 5.23; Cl, 16.86; N, 26.60. Found: C, 51.37; H, 5.35; Cl, 17.19; N, 26.63.

3,5-Diamino-1-phenethylpyrazole Hydrochloride (IIIc).—To a solution of 1.48 g. (0.01 mole) of ethyl cyanoacetimidate hydrochloride[3,4] and 20 ml. of ethanol was added with stirring under nitrogen 1.4 g. (0.01 mole) of phenethylhydrazine.[6] After 30 min. the mixture was filtered, and the filtrate was evaporated under reduced pressure to a tan pasty solid. Two recrystallizations from acetonitrile gave 0.21 g. (9%) of colorless prisms, m.p. 160–162°. An additional recrystallization afforded the analytical sample, m.p. 160–161°, λ_{max}^{MeOH} 237 mμ (ϵ 13,300).

Anal. Calcd. for $C_{11}H_{15}ClN_4$: C, 55.35; H, 6.29; Cl, 14.88; N, 23.48. Found: C, 55.14; H, 6.42; Cl, 14.45; N, 23.97.

(5) Melting points were determined with a Hershberg apparatus and are uncorrected. Ultraviolet spectra were determined with a Cary 11 spectrophotometer. N.m.r. spectra were determined with a Varian Associates A-60 spectrometer by Mr. W. Fulmor and associates. Microanalyses were performed by Mr. L. M. Brancone and associates.
(6) Phenethylhydrazine, b.p. 108–113° (1–1.5 mm.), was liberated from the commercially available sulfate salt with ethanolic sodium methoxide.

The Synthesis of 2-Bromopyrimidines and 2,2′-Bipyrimidines

DONALD D. BLY[1,2]

Department of Chemistry, Purdue University, Lafayette, Indiana

Received August 21, 1963

The syntheses of 2-bromopyrimidine and 2,2′-bipyrimidine have been reported recently,[3] as well as a study of 2,2′-bipyrimidine as a color forming agent in analytical chemistry.[4] The purpose of the present study was to determine whether the reverse addition diazotization method for converting 2-aminopyrimidine to 2-bromopyrimidine[3] could be generalized for preparing new substituted 2-bromopyrimidines, and to determine whether the resulting substituted 2-bromopyrimidines could, in general, be coupled, with the elimination of bromine, to form new substituted 2,2′-bipyrimidines.

This study was successful as far as it was carried out. Additional work on the project had to be suspended,

(1) The author gratefully acknowledges a postdoctoral fellowship granted to him by Eli Lilly and Co., which financially supported this work.
(2) To whom correspondence should be addressed at Carothers Research Laboratory, E. I. du Pont de Nemours and Co., Experimental Station, Wilmington, Del.
(3) D. D. Bly and M. G. Mellon, *J. Org. Chem.*, **27**, 2945 (1962).
(4) D. D. Bly and M. G. Mellon, *Anal. Chem.*, **35**, 1386 (1963).

because, despite the use of rubber gloves and aprons, the author developed a high sensitivity to 2-bromo-4-chloro-6-methylpyrimidine, resulting in severe contact dermatitis on the hands; but, as a result of the study, it is felt that the diazotization and coupling reactions are general for nontautomeric pyrimidines, it being necessary only to vary the conditions somewhat for the individual compounds.

The large excess of inorganic reagents and long reaction times required in the reverse addition diazotization reactions are evidently due to the fact that the respective amines are only very slightly soluble in water and the contact between the reactants is poor. However, no other solvent system could be found which would adequately dissolve all of the reagents and reactants. In order to maintain a high concentration of nitrous acid for a long reaction time, the hydrobromic acid was introduced at a constant, very slow, drop rate by a pressure-controlled dropping capillary, and the temperature of the reaction vessel was maintained constant with a Wilkens Anderson Low Temp bath.

The infrared spectra of all the pyrimidines, determined on a Perkin-Elmer Model 221 instrument with sodium chloride optics, were consistent with proposed structures. In the visible region, the 4,4′,6,6′-tetramethyl-2,2′-bipyrimidine gave a deep red color upon warming with a dilute solution of Cu(I), but formed no colored complex with Fe(II) or Fe(III). The ultraviolet spectra were determined on a Cary Model 10–11 spectrophotometer in distilled water using a distilled water reference.

Experimental[5]

Preparation of 2-Bromo-4,6-dimethylpyrimidine by Reverse Addition Diazotization.—A 24-g. quantity (0.214 mole) of 2-amino-4,6-dimethylpyrimidine was diazotized by the very slow addition of 114 ml. (1 mole) of concentrated hydrobromic acid to a solution containing the pyrimidine, 300 ml. of water, 300 g. of sodium bromide, and 70 g. (1 mole) of sodium nitrite at −3.2°. The addition of the acid took 24 hr. to completion.

The solution was then cleared of nitrogen oxides by an air stream, made strongly alkaline with cold 30% sodium hydroxide, and filtered. The precipitate and filtrate were each extracted with two 200-ml. portions of carbon tetrachloride and the extracts combined and evaporated to dryness. The residue was taken up in hot petroleum ether (b.p. 90–100°), cooled to 0°, and filtered. The filtrate was evaporated to give 9.4 g. (0.05 mole, 24%) of crystalline 2-bromo-4,6-dimethylpyrimidine. The product was further purified by sublimation *in vacuo* to give white crystals, m.p. 69.5–71.5°, a molecular weight of 183 (theory 187) as determined in chloroform by a Mechrolab osmometer, Model 301 A, and λ_{max} 256 and 217 mμ with log a_m = 3.62 and 3.83, respectively.

Anal. Calcd. for $C_6H_7BrN_2$: C, 38.5; H, 3.75; Br, 42.7; N, 15.0. Found: C, 38.5; H, 3.8; Br, 42.4; N, 15.2.

Scale-up of this reaction failed owing to very marked increase in foaming in the reaction mixture. The 4,6-dimethyl-2-pyrimidinol, also a product of the diazotization reaction, was isolated by adjusting the chloroform-extracted aqueous solution to pH 4.5, evaporating to dryness *in vacuo*, as with 2-pyrimidinol,[3] and extracting with hot ethyl acetate.

Preparation of 2-Bromo-4-chloro-6-methylpyrimidine by Reverse Addition Diazotization.—In like manner 2-amino-4-chloro-6-methylpyrimidine was diazotized by adding 228 ml. (2 moles) of concentrated hydrobromic acid to 40 g. (0.279 mole) of the pyrimidine mixed with 325 ml. of water, 300 g. of sodium bromide, and 140 g. (2 moles) of sodium nitrite at −3.2°. The addition of the acid took 44 hr. to completion.

After adjusting the solution to pH 7, the product was steam distilled, then crystallized from minimum petroleum ether (b.p. 60–70°) and vacuum dried to give 9.5 g. (0.049 mole, 16%) of crystalline 2-bromo-4-chloro-6-methylpyrimidine, m.p. 33–34°, molecular weight in chloroform of 210 (theory 208), and λ_{max} 260 and 217 mμ with log a_m = 3.68 and 3.85, respectively.

Anal. Calcd. for $C_5H_4BrClN_2$: C, 28.9; H, 1.9; Br, 38.1; Cl, 17.2; N, 13.5. Found: C, 28.9; H, 1.7; Br, 38.1; Cl, 17.2; N, 13.6.

The 4-chloro-6-methyl-2-pyrimidinol, also a product of the diazotization, floats to the top of the warm crude reaction mixture before steam distillation and can be skimmed off.

Preparation of 4,4′,6,6′-Tetramethyl-2,2′-bipyrimidine.—The experimental details were similar to those for 2,2′-bipyrimidine,[3] except that no nitrogen was used. A 20-g. (0.3 g.-atom) portion of activated[6] Natural Copper Fine 44-F was added all at once to 10 g. (0.053 mole) of 2-bromo-4,6-dimethylpyrimidine at reflux in 60 ml. of (calcium hydride-distilled) dimethylformamide. After 8 hr. of stirring at reflux, 5 g. of additional activated copper was added. After 24 hr. the mixture was cooled to room temperature, suction filtered, and the residue washed with a little water. The copper-product residue was then twice extracted for 2 min., respectively, with 200 ml. of concentrated ammonium hydroxide saturated with potassium cyanide. Each extraction was separated by suction filtration, and the combined filtrates then extracted with two 500-ml. portions of chloroform. The remaining copper residue was extracted once with chloroform.

The combined chloroform solutions were evaporated to dryness. The tarry residue was dissolved in 200 ml. of hot ethyl acetate, decolorized with Darco, filtered, and evaporated to yield 2.3 g. (0.01 mole, 26%) of tan, amorphous 4,4′,6,6′-tetramethyl-2,2′-bipyrimidine. Sublimation did not give a pure product, but constant m.p. 131–132° was obtained by crystallizing the sublimed material from an ethyl acetate–petroleum ether solution. [The pyrimidine was dissolved in minimum hot ethyl acetate, hot petroleum ether (b.p. 90–100°) added until the solution was cloudy, and the mixture cooled to 0° and filtered.] The molecular weight, determined in chloroform as above, was 213 (theory 214) with λ_{max} at 248 mμ and log a_m = 4.17.

Anal. Calcd. for $C_{12}H_{14}N_4$: C, 67.4; H, 6.6; N, 26.2. Found: C, 65.1; H, 6.9; N, 26.1.

Attempted Synthesis of 4,4′-Dichloro-6,6′-dimethyl-2,2′-bipyrimidine.—It was attempted to prepare this compound by a procedure exactly analogous to the synthesis of 4,4′,6,6′-tetramethyl-2,2′-bipyrimidine, and a reaction definitely took place on two different attempts. However, no one product was isolated, and the author had to give up the project due to his high sensitivity to the starting material. It is felt, however, that 4,4′-dichloro-6,6′-dimethyl-2,2′-bipyrimidine could be obtained, since the chlorine atoms should not interfere.[3]

(5) All melting points are uncorrected.

(6) E. C. Kleiderer and R. Adams, *J. Am. Chem. Soc.*, **55**, 4219 (1933).

Deuterium Exchange in the Pyridoxal-Leucine System[1]

G. A. JUNK AND H. J. SVEC

Institute for Atomic Research and Department of Chemistry, Iowa State University, Ames, Iowa

April 15, 1963

Deuterium exchange from a D_2O solvent is frequently used to confirm reaction mechanisms. The positions at which exchanges occur must be determined, and the total amount of deuterium incorporated at each position should be measured. These values then can be used to support or disprove a particular mechanism. A convenient procedure for accurate and direct determinations of both the location and extent of deuterium incorporated in a molecule uses mass spectral fragmentation data. A detailed discussion of the use

(1) Contribution no. 1297. Work was performed in the Ames Laboratory of the U. S. Atomic Energy Commission.